samples, and inter- and intra-observer error. For this reason, several simple non-invasive clinical scoring systems have been proposed to diagnose advanced fibrosis in NAFLD [1].

We read with great interest the article by Ruffillo *et al.* that compares the NAFLD fibrosis score and BARD score in predicting fibrosis in NAFLD [2]. In their retrospective analysis, they concluded that both scoring systems were similar in NAFLD. The results are interesting and likely to contribute to our understanding of this issue; however, we have some concerns about the data presented by the authors.

Firstly, as mentioned in the text, the presence of impaired fasting glucose (IFG) or diabetes mellitus (DM) is a component of the NAFLD fibrosis score. Although it was stated in the article that some of the patients were diabetic at baseline, there is no information regarding the glucose tolerance status of the other subjects. It is well known that NAFLD is strongly associated with obesity, hypertension, dyslipidemia and also glucose tolerance abnormalities [3,4]. In addition, all these metabolic problems are risk factors for DM and also prediabetes, namely IFG and impaired glucose tolerance (IGT). In light of these data, we think that some of the study participants may still have overt glucose dysregulation or DM without implementation of the glucose tolerance test. Secondly, no information about the medications was given in the text. Yet, we know that liver enzymes are easily affected by medications started for the metabolic problems mentioned above [5,6]. This issue is important because AST/ALT ratio is another variable in the NAFLD fibrosis score.

We conclude that the presence of major confounders raises some questions about the data presented, and as such some of the resulting interpretations should be taken with caution. In such a case, statistical correlations may also be misleading. It would be appreciated if the authors could present some more data adjusted for the topics mentioned above. This could provide the readers of the journal clearer information in the prediction of fibrosis by NAFLD fibrosis score in this clinically relevant condition.

Conflict of interest

The authors declare that they do not have anything to disclose regarding funding or conflict of interest with respect to this Letter.

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Reply to: "Non-invasive prediction of fibrosis in nonalcoholic fatty liver disease"

To the Editor:

We would like to address the concerns presented by Dr. Dogru *et al.* in their letter to the Editor. The first issue commented on pertains to one of the six variables included in the formula of the NAFLD fibrosis score: impaired fasting glucose/diabetes. For that variable, we took the same definition from the original paper by Angulo *et al.* [1]. Diabetes was defined as a fasting glucose level $\geqslant$126 mg/dl or a patient who was already under treatment with anti-diabetic drugs; and impaired fasting glucose, as a fasting glucose level $\geqslant$110 mg/dl. We did not perform any glucose tolerance test in our patients. As stated in our paper [3], we just retrospectively analyzed data of consecutive patients with biopsy proven NAFLD that had been prospectively collected. One advantage of both, the NAFLD fibrosis score and the BARD score [2], is that they include 6 and 3, respectively, easily available variables. Being a group that is especially interested in research on NAFLD, we had all of these variables available in our database. In fact, at present if we wanted to repeat the analysis of comparison between both scoring systems, data on 182 biopsy proven NAFLD patients would be available (instead of 138 in our published paper).

The second concern raises the point about the lack of information on medications that patients could be receiving. We agree that some drugs may influence the serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and we do not have the complete information about medications taken by our patients. Some of them were receiving antihypertensive drugs such as enalapril, or antihyperlipidemic drugs such as statins. However, the pattern of liver enzymes in our NAFLD patients conformed to those commonly found; with a mild to moderate elevation and an ALT predominance. Median ALT was 69 IU/L, interquartile

range 50–96.5 IU/L and, in only 4 out of 138 patients (2.9%), levels above 200 IU/L (that is, five times above upper limit of normal) were found (maximal value, 294). AST/ALT ratios in these 4 patients were 0.61, 0.52, 0.78 and 0.55, similar to the whole group of patients. Thus, we might suggest that most of the patients were not showing a drug-induced liver injury able to modify AST or ALT levels. The AST/ALT ratio is a very important variable, strongly associated with the presence of advanced fibrosis in the univariate analysis (with higher odds ratio than other variables) and therefore, is included in both scoring systems, the NAFLD fibrosis score and the BARD score. Furthermore, in the BARD score, an AST/ALT ratio $\geqslant$0.8 sums 2 points while the other two variables, presence of diabetes or body mass index $\geqslant$28, sum only 1 point. However, the information on the list of medications taken by the patients is also lacking in the two original studies [1,2].

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Gender disparity and MELD in liver transplantation

To the Editor:
We read with great interest the paper by Myers *et al.* [1], recently published in *Journal of Hepatology*, regarding the disparities between males and females in the MELD-based allocation system for liver transplantation. The authors found that women are disadvantaged under MELD, which may be attributable to the use of serum creatinine (Cr) in MELD score equation [1]. This confirms our previously published work indicating a systematic bias against women [2]. It is known that Cr is an inaccurate marker of renal function, since its concentration is influenced by several factors unrelated to renal function, such as total muscle mass, leading to discrepancies in Cr concentration between individuals with the same renal function [same glomerular filtration rate (GFR)] but of different age, race and sex [3].

We showed that Cr and GFR in females were lower than males, and female gender might negatively influence the chances of receiving a liver transplant with respect to men [2]. Correcting Cr by equalising the GFR between men and women, resulted in an increase in MELD score by up to 3 points in female LT candidates [2]. Following this, Moylan *et al.* evaluated the UNOS database [4] and showed that women were more likely to die on the waiting list in the post-MELD era, compared to the pre-MELD one, although women were listed with lower median MELD scores, compared to men (14 *vs.* 15, p <0.001) [4]. In the UNOS database, Myers *et al.* [1] found the same discrepancies, as we did [2]: women, compared with men, had lower Cr (0.9 *vs.* 1.0 mg/dl, and MELD 16.5 *vs.* 17.2, both p <0.001), but worse renal function (estimated GFR: 72 *vs.* 83 mL/min, p <0.001); however they were less likely to undergo liver transplantation (LT), and had greater 3-month mortality. Interestingly, Myers *et al.* [1] also found that patients with cirrhosis with a black ethnicity had a lower mortality, compared to white ethnicity. We believe that this likely to be related to Cr: black patients as a group have a higher Cr (more muscle mass), compared to white, for the same renal function, and, thus, MELD score may overestimate the severity of their liver disease. Indeed, MDRD calculations of GFR commonly have a correction factor for black race.

However Myers *et al.* did not find that using a calculated GFR (eGFR based on MDRD formula) helped to discriminate a different prognosis for men *vs.* women [1]. However, the evaluation with eGFR (MDRD formula), and not with "true" GFR using a gold standard method, could explain the discrepant results regarding the comparison presented of MELD-(Sodium)-eGFR and MELD-(Sodium) as the authors themselves suggested [1]. In contrast, Lim *et al.* [5] (using ^{125}I-iothalamate for true GFR) found that "true" GFR was superior to Cr in assessing mortality risk on the waiting list and its incorporation in the MELD score (in the place of Cr), led to a significant improvement of discriminative ability of MELD. Unfortunately, Lim *et al.* [5] did not evaluate the prognostic impact of MELD-Cr and MELD-GFR scores in men and women candidates separately.

Secondly, it is possible that the higher mortality of women placed on waiting lists for liver transplantation [1,4], compared to men, could be related to the presence of significant differences for matching of donor organ size to either recipient men or women, and thus, longer waiting times for women compared to men. Unfortunately, Myers *et al.* [1] did not evaluate this parameter. However, Lai *et al.* [6] recently suggested that height contributes to the gender disparity, possibly reflecting differences in transplantation rates for shorter individuals. The authors